Childhood trauma associated white matter abnormalities in first-episode schizophrenia

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Abstract

Schizophrenia is associated with brain connection irregularities within and between brain regions. Childhood trauma increases the risk of schizophrenia suggesting that the relationships between childhood trauma and brain connectivity requires further investigation. Here, we examine the relationship between childhood trauma (as measured by the Childhood Trauma Questionnaire) and fractional anisotropy (FA) in 54 minimally treated first-episode schizophrenia patients and 51 community matched controls. Patients who experienced high levels of trauma had significantly lower FA in the inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and inferior fronto-occipital fasciculus (IFOF) compared to controls who experienced high levels of childhood trauma. A history of childhood sexual abuse in patients was associated with lower FA in the IFOF, ILF, SLF and forceps major compared to patients without a history of sexual abuse. However, patients who had experienced childhood emotional neglect had higher FA in the right SLF compared to patients with low levels of emotional neglect. Our findings highlight altered cortico-limbic circuitry in first-episode schizophrenia patients compared to controls and differential effects of childhood emotional neglect and sexual abuse on white matter in patients. Although stress-related WM pathways appear to be involved in both schizophrenia and otherwise healthy controls previously exposed to childhood trauma, the pattern of disruption of WM integrity in FES patients appears to be distinct.

Keywords

abuse/neglect/diffusion tensor imaging

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1. Introduction

There is a well-established link between childhood trauma and schizophrenia. A history of childhood trauma both increases the risk of developing psychosis,[1] and is associated with greater co-morbidity,[2] more cognitive impairment[3] and persistence of symptoms over time.[4] Childhood trauma denotes a range of possible severe adverse experiences, including sexual, physical and emotional abuse, and physical and emotional neglect.[5] One possible explanation for the association is that childhood is a sensitive developmental period and childhood trauma, through psychological or biological mechanisms, interferes with normal neurodevelopment, thereby establishing a biological vulnerability in affected individuals.[6]

Indeed, adults with histories of childhood maltreatment have lower grey matter volumes in the anterior cingulate, prefrontal cortex, corpus callosum and hippocampus, higher amygdala reactivity to emotional faces and diminished striatal response to anticipated rewards than non-maltreated comparison subjects (for review see Teicher and Samson, 2016).[7] Although the biological mechanisms that underlie these associations remain unclear, the evidence to date suggests that a history of childhood maltreatment is associated with disruption of the development and functioning of the HPA axis and may sensitise neurobiological systems implicated in stress adaptation and response thereby shaping neural structure and functioning.[8–10] Childhood adversity may have a broad impact on neurodevelopment via a cascade of stress-mediated effects on hormones and neurotransmitters that shape neurogenesis, synaptic overproduction, pruning, and myelination during sensitive periods in genetically susceptible individuals, affecting stress-vulnerable brain regions such as the hippocampus, amygdala, neocortex, and white matter tracts.[7,11] White matter abnormalities described in healthy participants who experienced childhood trauma complement the findings of brain morphological studies.

The microstructural properties of white matter tracts are usually studied in vivo with diffusion tensor imaging (DTI), an approach that provides a number of measures of white matter

integrity, of which Fractional Anisotropy (FA) is probably the most commonly reported.[12] FA values are thought to reflect both myelination and organization of fibre tracts that form the basis of brain connections.[13] A history of childhood trauma has been associated with white matter abnormalities in otherwise healthy participants, with a predilection for the corpus callosum and cortico-limbic tracts.[14]

Psychiatrically healthy adults with a history of childhood trauma have shown reduced FA in the corpus callosum, corona radiata, cingulum hippocampus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus.[14] Decreased FA in frontal and temporal white matter regions, including in the uncinate fasciculus, superior longitudinal fasciculus, and arcuate fasciculus, has been described in children with a history of early social deprivation.[15] Adolescents who had experienced early childhood neglect showed lower FA values in the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, corticospinal tract, cingulum, anterior corona radiata as well as greater FA in anterior thalamic radiation and forceps minor compared with comparison adolescents who had not experienced neglect.[16]

Considering the role of childhood trauma in increasing the risk of schizophrenia, the relationships between childhood trauma and brain connectivity in schizophrenia are of interest. Schizophrenia has been characterised as a disorder of brain connectivity,[17–20] and several studies have demonstrated a disruption in the trajectory of white matter (WM) development in psychotic and clinical high risk samples.[21–23] There is also growing evidence that childhood and adolescence are sensitive stress exposure periods when structures and pathways impacted by trauma are most vulnerable resulting in an alteration in trajectories of brain development.[7,11]

To our knowledge, there is only one known neuroimaging study that has examined the integrity of white matter tracts in people with schizophrenia who have experienced childhood trauma.[24] In a cohort of 83 patients with chronic schizophrenia, Poletti et al reported an association between an adverse early familial environment and reduced FA in the corpus

callosum, left cingulum, left corona radiata, bilateral superior longitudinal fasciculus and left anterior thalamic radiation. Although these findings suggest the presence of a set of brain alterations common to both schizophrenia patients and non-clinical samples who have experienced childhood adversity, the lack of control group, the long illness duration and medication exposure limit the generalizability of these findings. Furthermore, the study used the Risky Family Questionnaire total score as a single measure of familial conflict, neglect and abuse and did not differentiate between trauma types, which may have differential effects. For example a history of childhood abuse is more pronounced for persistent positive symptoms, while neglect is associated with more general psychopathology.[25,26] There is also some evidence that there may be a greater association between psychosis and physical abuse than with other adverse childhood experiences.[27]

This study examined whether DTI measures of WM tracts are associated with childhood trauma in first episode schizophrenia (FES). We used tract based spatial statistics (TBSS) to examine the relationship between childhood trauma and fractional anisotropy in FES patients (n=54) and healthy controls (n=51) recruited from the same geographical areas. Firstly, we hypothesized that childhood trauma related FA abnormalities would have a predilection for stress sensitive cortico-limbic tracts and the corpus callosum in patients and in controls. Next we hypothesized that these abnormalities would be greater in patients who experienced childhood trauma than in controls who experienced childhood trauma. Finally, we performed an exploratory analysis examining whether trauma subtypes had differential effects on white matter connectivity in patients.

2. Methods

2.1 Participants

The sample comprised 77 minimally treated first-episode schizophrenia patients and 51 matched controls as part of a study examining clinical, biological and functional outcome of FES in Cape Town, South Africa. Patients were recruited from inpatient services at Tygerberg and Stikland Hospital, and related community clinics in Cape Town, South Africa. For inclusion in the study, patients had to be aged 16 to 45 years, and experiencing a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder based on the Structured Clinical Interview for DSM-IV (SCID) –

Patient Edition.[28] The healthy control group was matched for age, sex, ethnicity and level of education (Table 1), and had no current DSM-IV axis I or II disorder as determined by the by SCID-Non-Patient Edition interviews. Healthy controls were neighbourhood contacts of the families of the patients with FES and, in addition, advertisements were placed in community centers in the same catchment area as the patients. Patients and controls were excluded if they had a serious or unstable general medical condition, mental retardation, current substance abuse(as confirmed by history taking of abuse in the past month), or recent substance use that could influence the participant's current mental state (as confirmed by history taking or positive urine drug screen), and less than 7 completed years of schooling. Patients and caregivers were interviewed to corroborate patient histories. Patients were excluded if they had a lifetime exposure to > 4 weeks of antipsychotic medication or were previously treated with a long-acting depot antipsychotic. Each patient was carefully screened with a thorough physical examination and review of the medical history, ECG, urine toxicology screen and structured assessment of symptoms to verify that inclusion criteria were met. Duration of untreated psychosis (DUP) was estimated from the onset of continuous positive psychotic symptoms to initiation of adequate treatment. Adequate treatment was defined as the start of structured treatment with antipsychotic medication. Controls were excluded if they had a first degree relative with a psychotic disorder. Patients and controls were compensated for transport costs incurred during their participation in the study, but did not receive any other financial reward.

This study was conducted according to the principles of the Declaration of Helsinki 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/). After the study procedures were fully explained in accordance with the ethical guidelines of the institutional review board, participants provided written informed consent. The parent study was registered on the South African National Clinical Trials Register (www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx), trial number DOH-27-0710-1957.

2.2 Clinical rating scales

Diagnosis was assessed with the Structured Clinical Interview for DSM-IV [SCID].[28] Severity of psychotic symptoms was assessed using the complete Positive and Negative Syndrome Scale (PANSS).[29] Diagnosis and clinical assessment was determined by trained physicians,

and inter-rater reliability testing was conducted periodically for the PANSS (intraclass correlation 0.7 or higher).

Participants and controls were assessed with the Childhood Trauma Questionnaire (CTQ) short form, a self-administered inventory that has demonstrated reliable and valid retrospective assessment of child abuse and neglect.[30] The instrument has 28 Likert-type items (25 clinical symptom items and 3 validity items to identify underreporting), and 5 subscales (sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect). Subscale scores range from 5-25 and the scale also yields a total score which is the sum of the 5 subscales ranging from 25-125.[30] We included subscale and total scores in the analyses. Of the 77 first-episode schizophrenia patients who completed the childhood trauma questionnaire, 16 were excluded from the neuroimaging component because we applied for ethics approval for the MRI component once recruitment of patients in the parent study had already begun. A further 4 were excluded because of motion artefacts and 4 were unable to be scanned because of claustrophobia. Of the 52 controls, 1 was excluded due to motion artefacts.

2.3 Image acquisition

We acquired diffusion-weighted images (DWIs) on a 3.0 T Siemens Allegra MRI scanner (Erlangen), Germany with the following parameters: field of view= 220m, spatial resolution 1.8X1.8X1.8mm^3, repetition time= 8800ms, echo time 88ms, 65 slices, no distance factor with twofold GRAPPA acceleration. The gradients were applied in 30 directions with b=1000s/mm ^{2} and a single unweighted volume (b=0s/mm2) were also acquired. The sequence was repeated three times.

2.4 Image pre-processing

The DWIs were pre-processed using the Functional MRI of the Brain (FMRIB) Software Library (FSL) version 4.1.8 (www.fmrib.ox.ac.uk/fsl/)[31] Raw DTI data were corrected for eddy current distortions and head motion, and the images were imported into Matlab.[32] The three

acquisitions were co-registered by using the first b=0 mm/s^2 as the reference image. Outliers were determined by calculating the Z-value of the tensor estimates at the 25th and 75th percentiles. Data points falling outside of more than 3 standard deviations were discarded. The acquisitions were then averaged and exported to the FSL for further processing.

2.5 MRI analysis

Using FSL's Randomize tool, permutation-based inferences with Threshold-Free Cluster Enhancement (TFCE) were carried out for voxelwise analysis of FA data.[33] Tract-based spatial statistics (TBSS) version 1.2 was used for voxelwise analysis of the preprocessed FA data. First, individual FA images were aligned to the FMRIB58_ FA standard-space image, using nonlinear registration. Next, the mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the entire group. The mean FA skeleton was then thresholded at a FA value of ≥0.4, to exclude peripheral tracts and minimize partial voluming. Finally, each participant's aligned FA images were projected onto the mean FA skeleton and the resulting data were fed into voxelwise permutation-based analysis. The resulting statistical maps were corrected for multiple comparisons across space ($p < 0.05$) and the JHU White Matter and Juelich Histological atlases were used to label clusters with significant FA alterations.

2.6 Statistical analysis

We used analysis of t-tests and chi square tests to compare age, gender, and education in patients and controls. The CTQ total and subscales were not normally distributed; therefore, we used a median-split approach to dichotomise scores into high/low severity of trauma. For our primary analyses, we performed whole brain analyses examining for overall FA differences between all FEP patients and controls and compared FA between those who had high levels of overall childhood trauma and those who had low levels. We thereafter performed post-hoc analyses comparing those who had high levels of trauma subtypes (sexual abuse, physical abuse, physical neglect, emotional neglect, emotional abuse) in various groups (within patients, between patients and controls and within controls). We

assessed for between group (patient and control) interaction.

3. Results

3.1 Participant characteristics

The clinical and demographic features are presented in Table 1. Age, gender, education and ethnicity were similar in patients and controls. Patients and controls had comparable CTQ total and subscale scores. In keeping with the high levels of community violence experienced by our cohort, there was no significant difference in the number of patients and controls with high levels of overall trauma and trauma subtypes (reported previously).[34,35] FA values were significantly lower in FES patients compared to controls, as published in detail elsewhere.[36]

3.2 Fractional anisotropy and childhood trauma in patients and controls

3.2.1 Patients versus controls

Total childhood trauma: Compared to matched controls who experienced high levels of CT, FES patients who experienced high levels of CT had significantly lower FA in a cluster centred in the left inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF), as well as a cluster in the right SLF and inferior fronto-occipital fasciculus (IFOF) (Table 2).

Childhood trauma subtypes: There was no difference in FA between patients and controls who experienced high levels of childhood trauma for any of the subscales.

3.2.2 Within patient group

Total childhood trauma: There was no significant difference in FA in any tract between FES patients who experienced high levels of overall CT and FES patients who experienced low levels of CT.

Childhood trauma subtypes: FES patients with high levels of childhood sexual abuse had *lower* FA in a cluster comprising the right IFOF, ILF, and forceps major compared to FES patients without a history of sexual abuse (Table 3). On the other hand, FES patients with a history of high levels of childhood emotional neglect, had *higher* FA in the right SLF compared to FES patients with low levels of childhood emotional neglect (Table 4). There were no

significant differences in FA between FES patients who experienced high levels of physical neglect, physical abuse and emotional abuse compared to FES patients who experienced low levels.

3.2.3 Within control group

Total childhood trauma: There was no significant difference in FA in any tract between controls who experienced high levels of overall CT and controls who experienced low levels of CT.

Childhood trauma subtypes: There was no difference in FA between controls who experienced high levels and those controls who experienced low levels of childhood trauma in any of the subscales.

4. Discussion

Here, we investigated associations between white matter FA and childhood trauma in people with FES and in matched community controls. A key finding of our study is that FA of the ILF, SLF and IFOF is lower in childhood trauma exposed patients than in childhood trauma exposed controls. These WM tracts have been shown to be compromised in schizophrenia[37,38] and also known to be affected by childhood trauma[7,14,39,40] which may point to biological markers of vulnerability and resilience to schizophrenia in childhood trauma exposed individuals.

Our findings are in keeping with the only known previous study that examined DTI abnormalities related to childhood adversity in schizophrenia.[24] The authors found that, in 83 patients with chronic schizophrenia, higher exposure to harsh parenting was associated with lower FA in the bilateral SLF, left ILF, left cingulum, corpus callosum, left cingulum, left corona radiata, and left anterior thalamic radiation, although the lack of control group and illness chronicity limits the generalizability of these findings.

The disconnection hypothesis proposes that, in schizophrenia, there is dysfunctional integration in distributed but circumscribed neuronal systems that leads to neuromodulatory failure, e.g. mesocorticolimbic dysconnectivity.[41] The ILF, SLF and IFOF are important cortico-limbic tracts that are implicated in the pathophysiology of schizophrenia.[42,43] The IFOF

directly interconnects the occipital, posterior temporal and the orbito-frontal areas while the ILF connects similar brain areas indirectly, and is an important source of fibres afferent to the amygdala and hippocampus.[44–46] The amygdala, hippocampus, prefrontal cortex and related pathways are integral to emotional response, fear modulation and memory. The involvement of the ILF, SLF and IFO in both childhood trauma and schizophrenia suggests that limbic circuitry may be particularly vulnerable to long-term consequences of childhood maltreatment in schizophrenia.

A further important finding of our study is that FA was lower in FES patients with a history of childhood sexual abuse compared to FES patients without a history of sexual abuse. Furthermore, FES patients who had experienced childhood emotional neglect had higher FA compared to patients without emotional neglect. These findings are consistent with the proposal that trauma types have differential effects on neurodevelopment and that childhood abuse and neglect lie along independent pathways to psychosis.[25,26] McLaughlin and colleagues[47] suggest that threat (e.g. sexual abuse) and deprivation (e.g. emotional neglect) are distinct dimensions of the environmental experience and may have distinct effects on neural development.

FES patients with a history of sexual abuse had lower FA in clusters involving the IFOF, ILF, SLF and forceps major than patients without a history of sexual abuse. Whether sexual abuse exerts effects that can be differentiated from the effects of physical and emotional abuse remains to be determined. It could be speculated that sexual abuse is particularly pernicious and impactful on the developmental trajectory, resulting in specific neuroplastic adaptive changes. These adaptations, for example reduced synaptic density, may initially be protective in that it shields a child by gating sensory processing.[48] However, later in life, these impaired neurobiological substrates may predispose to the development of disorders.[48]

The finding of higher FA in the SLF in FES patients who experienced childhood emotional neglect compared to patients who did not experience emotional neglect is unanticipated, but does lend support to the theory that childhood abuse and neglect may lie on independent

neurobiological pathways to psychosis. [25,35,49] Exposure to early stress may prompt adaptive brain development along alternative developmental pathways to enable survival in a stress filled world.[11] SLF is a late maturing tract and so may be differentially vulnerable to the effects of emotional neglect.

Strengths of our study include the inclusion of first-episode, minimally treated patients, which allowed us to largely eliminate the effect of treatment and illness chronicity as well as the inclusion of matched community controls who reported similar levels of childhood trauma exposure. We assessed the effect of different types of childhood trauma and used a well-validated measurement of childhood trauma. Several limitations should be noted. The CTQ is a retrospective self-rated instrument and subjective processes such as current mental health and self-rated perception of health may contribute to individual discrepancies in retrospective reporting of trauma.[50] The nature of the trauma could not be explored in depth, nor does the CTQ assess the frequency of trauma and the age at which trauma first occurred. The CTQ does not assess other forms of childhood adversities such as witnessing domestic violence and bullying, the latter is hypothesized to be associated with psychosis.[51] We did not assess for the interaction effects of gender, ethnicity and substance use on whole brain analyses. Although we did not find a relationship between these variables and childhood trauma in patients and controls, these factors have been shown to be related to childhood trauma in other studies.[52]

This study provides important preliminary data that increase our understanding of the relationship between childhood trauma and schizophrenia. Our findings highlight altered cortico-limbic circuitry in FES patients compared to community controls and differential effects of childhood emotional neglect and sexual abuse on white matter in FES patients. Although previous studies have found that stress related WM pathways appear to be involved in both chronic schizophrenia[24] and otherwise healthy controls previously exposed to childhood trauma,[14–16] the pattern of disruption of WM integrity in FES patients appears to be distinct.

Future studies should focus on resilience factors to address why some individuals exposed to childhood trauma develop schizophrenia while others do not. It is also important to explore

whether brain changes associated with childhood trauma in schizophrenia patients are correlated with clinical, cognitive and functional outcomes, while taking into account the possible confounding effects of age of onset of childhood trauma, cumulative trauma load, gender, age of onset and duration of psychosis, and treatment status. It would also be important to examine whether clinical symptoms in patient vary according to trauma subtypes and whether these differences influence DTI measurement. Finally, future research should consider critical periods during which the brain is particularly susceptible to both the impact of childhood trauma as well the development of schizophrenia.

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Conflict of interest

RE has received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Organon, Pfizer, Servier, Otsuka and Wyeth for participating in advisory boards and speaking at educational meetings, and has received research funding from Janssen, Lundbeck and AstraZeneca. BC has received honoraria from Sandoz and Janssen for speaking at educational meetings. SS has received speaker's honoraria and travel sponsorship from Lundbeck, Servier, Cipla, Sanofi, and Dr Reddy's. LA, SdP, FS, SK, JPF and PD report no conflict of interest.

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Table 1: Demographic and clinical characteristics for first-episode schizophrenia and control groups

Characteristic	**All participants**		**Analysis**		
	FES (n=54)	**Controls (n=51)**			
			test statistic	df	p
Male sex, n (%)	40(74)	35(67)			.07
Age (mean, SD)	24.78 (6.98)	25.04 (6.85)	t=.96	103	.35
Education (years)	9.9 (1.9)	10.3 (1.5)	t=-1.93	103	.11
Ethnicity n(%)			x^2=2.99		.22
Black	0 (0)	6(15.79)			
Mixed race	15 (93.75)	29 (76.31)			
White	1 (6.25)	3 (7.89)			
CTQ, median [range]					
Emotional neglect	12[5-25]	9.5[5-24]	z=-.821		.41
Physical abuse	7[5-23]	7[5-25]	z=-.194		.84
Emotional abuse	9[5-22]	9[5-25]	z=.413		.68
Physical neglect	9[5-22]	8.5[5-17]	z=-.88		.38
Sexual abuse	5[5-25]	5[5-25]	z=.390		.70
Total score	46.5[25-92]	43[25-93]	z=-.225		.82
CTQ, High (%)*					
Emotional neglect	17(32.69)	14.26.92)			.64
Physical abuse	20(38.46)	15(28.8)			.41
Emotional abuse	15(28)	13(25.0)			.96
Physical neglect	26(48.15)	22(42.31)			.65
Sexual abuse	13(24.53)	14(26.92)			.85
Total score	16(29.63)	13(25.00)			.70
	FES only (n=54)				
	CTQ total high (n=16)	CTQ total low (n=38)			
Age (mean, SD)	25.54 (7.68)	22.56 (5.42)	t=1.68	52	.10
Male sex, n(%)	13 (81.25)	27 (71.05)	x^2=0.61		.43
Ethnicity n(%)			x^2=2.99		.22
Black	0 (0)	6(15.79)			
Mixed race	15 (93.75)	29 (76.31)			
White	1 (6.25)	3 (7.89)			
Education (years)				52	
Substance abuse	9(56.25)	15(39.47)	x^2=1.28		.26
PANSS total score	94.2 (11.71)	92.32(14.53)	t=-1.16	51	.28
Antipsychotic naïve	8 (53.33)	18 (47.37)	x^2=.15		.70
DUP	39.39(46.80)	29.15(32.35)	t=-.91	51	.37

Table 2: Whole brain *lower* fractional anisotropy in FES patients with history of childhood trauma compared to FES matched controls with a history of childhood trauma.

Brain region	Tracts	Hem	Cluster size	MNI coordinates of voxel of maximum significance[a]			Probability
				x	*y*	*z*	
Cluster 1	Inferior longitudinal fasciculus, Sup long fasciculus (temporal part)	L	34	125	77	99	.04
Cluster 2	Sup long fasciculus (temporal part), Inferior fronto-occipital fasciculus	R	214	59	87	86	.04

Table 3: Whole brain *lower* fractional anisotropy in FES patients with history of childhood sexual abuse compared to FES patients without a history of sexual abuse

Brain region	Tracts	Hem	Cluster size	MNI coordinates of voxel of maximum significance[a]			Probability
				x	*y*	*z*	
Cluster 1	Inferior fronto-occipital, inferior longitudinal fasciculus, forceps major	R	971	61	58	85	.006
Cluster 2	Forceps major, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus	L	2793	111	74	84	.007

Table 4: Whole brain *higher* fractional anisotropy in FES patients with history of childhood emotional neglect compared to FES patients without a history of emotional neglect

Brain region	Tracts	Hem	Cluster size	MNI coordinates of voxel of maximum significance[a]			Probability
				x	*y*	*z*	
Cluster 1	Superior longitudinal fasciculus	R	4	63	84	115	.0001
Cluster 2	Superior longitudinal fasciculus	R	10	64	80	112	.0001
Cluster 3	Superior longitudinal fasciculus	R	21	53	93	100	.0001
Cluster 4	Superior longitudinal fasciculus	R	165	59	86	107	.001